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(54) Title: THE USE OF A VITAL DYE FOR FACILITATING SURGICAL PROCEDURES FOR CATARACT EXTRACTION

(57) Abstract

The invention relates to a method for performing a capsulorhexis, wherein a lens capsule is stained using at least one dye, which dye is capable of staining tissue without diffusing through said tissue.

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Title: The use of a vital dye for facilitating surgical procedures for cataract extraction

The invention relates to the field of ocular surgery, in particular to surgical procedures for cataract extraction.

In the normal eye, the crystalline lens is located behind the iris, and in front of the corpus vitreum. The lens 5 is transparent, biconvex, accounts for about 20 diopters of convergent refractive power of the eye, and it is composed of a capsule that encloses and encompasses the lens substance, i.e. the lens epithelium, the cortex, and the nucleus. A ring of zonular fibers, that extend from the ciliary body to the 10 anterior part of the lens capsule, keeps the lens positioned within the eye.

The capsule is an elastic, type IV collagen basement membrane produced by the lens epithelial cells. The thickness of the capsule varies from 4-24 μm , with a 15 thickness of about 14 μm at its anterior part, 24 μm at its equatorial part, and about 4 μm at its posterior part. Because of its transparency, and because its refractive index nearly equals the lens substance, the lens capsule 20 can not be discriminated from the lens substance, except with the use of a slit-lamp at high magnification.

The lens substance may become less transparent, i.e. a cataract may develop, due to aging or to a wide variety of ocular or systemic pathological disorders or diseases. Affected portions of the lens substance may differ with the 25 type of disorder, but in most cases the optical and/or refractive functions of the lens are compromised, for example a decreased visual acuity, a decreased contrast sensitivity, an accommodation loss, etc.

To restore the optical pathway, cataract surgery may 30 be performed to remove the opaque lenticular mass. Although various surgical techniques are available, extracapsular

cataract extraction techniques, the Blumenthal technique, or phacoemulsification are most often used. With all techniques, the anterior chamber of the eye is opened through a peripheral corneal, limbal or scleral incision, 5 the anterior lens capsule is opened, and the lens substance is removed, while leaving the peripheral rim of the anterior lens capsule as well as the capsular equatorial and posterior portions in-situ. The empty lens capsule forms a capsular 'bag' that can be used to support a 10 synthetic intraocular implant lens (IOL), so that an IOL is positioned 'in the bag'.

Various techniques are used to open the anterior lens capsule, i.e. the excision of a portion of the anterior lens capsule, with or without the use of a viscous or 15 viscoelastomeric substance, for example the can-opener technique, the envelop technique, the capsulotomy, and the continuous circular capsulorhexis. To visualize the capsular defect during the opening of the capsule, the red fundus reflex, the co-axial light of an operating 20 microscope that is reflected from the posterior pole of the eye, is commonly used. When retroillumination is absent, for example with dense cataracts, heavily pigmented fundi or a combination of both, it is often not or only hardly possible to discriminate the anterior capsule from the 25 underlying lens tissue.

Visualization of the defect in the anterior capsule during the opening of the lens capsule is an important step in the surgical procedure, because the mechanical traction forces which the capsule can withstand during surgery, vary 30 with the configuration of the capsular opening. For example, in phacoemulsification a continuous circular capsulorhexis is commonly performed, because a circular configuration of the capsular opening can withstand best the surgical manipulations within the lens capsule during 35 the removal of the lens substance. Improper visualization of the anterior lens capsule during the performance of a

capsulorhexis may be responsible for a risk of a radial tear toward or beyond the equator of the lens capsule, and associated complications, for example vitreous loss, or a dropped nucleus.

5 Furthermore, in a subsequent phase of the surgery the outline of the opening in the anterior lens capsule is often difficult to visualize. During the removal of the lens substance in phacoemulsification a useful red fundus reflex is nearly always absent, because the lenticular
10 tissue becomes opaque. However, during phacoemulsification it still is important that the rim of the capsulorhexis is not damaged, so that the capsular integrity is maintained during the surgical manipulations within the capsule. For example, an inadvertent touch of the rim with the tip of
15 the phacoemulsification hand piece or an overextension of the capsule during dividing the lenticular substance, may damage the rim of the capsulorhexis. Again, the damaged rim may give a greater risk of a radial tear toward the equator and associated complications, especially because the damage
20 to the rim of the capsulorhexis may not be noticed during surgery.

During implantation of an IOL, the rim of the anterior capsule must be visualized to place the haptics of the IOL in between the anterior and posterior portions of the lens
25 capsule. In this phase of the surgery, the anterior capsular rim can often be seen with the use of the red fundus reflex. To determine if a haptic(s) is positioned underneath the anterior capsular rim, the IOL is manipulated in such a way that the displacement of the
30 capsular rim by the haptic or optic of the IOL indicates the position of the IOL relative to the capsule. In cases where a useful red fundus reflex is absent, as mentioned above, it becomes difficult to determine the position of the IOL relative to the capsule. Thus, there is a risk of
35 the IOL being inserted in the area between the iris and the anterior lens capsule, for example the ciliary sulcus.

Improper positioning of an IOL (that was designed to fit into the capsular bag) may be complicated by dislocation of the IOL after surgery.

In a letter to the Editor of the Journal of Cataract and Refractive Surgery (Hoffer KJ, McFarland JE, "Intracameral subcapsular fluorescein staining for improved visualization during capsulorhexis in mature cataracts", J Cataract Refract Surg 1993;19:566), K.J. Hoffer and J.E. McFarland have addressed the above problems associated with the poor visibility of the anterior capsule during the performance of the capsulorhexis, in particular in the presence of a mature cataract. They suggest that the problems may be overcome by injecting a solution of fluorescein underneath the anterior chamber. During the capsulorhexis, the capsule would be better visible due to it being stained by the fluorescein dye.

Fluorescein is a dye which is capable of diffusing through various tissue structures (see e.g. Brubaker RF, "Clinical evaluation of the circulation of aqueous humor", in Tasman W, Jaeger EA, "Duane's clinical Ophthalmology", Volume 3, Chapter 46, Philadelphia, JB Lippencott Co, 1994:1-11; or Friberg TR, "Examination of the retina: principles of fluorescein angiography", in Albert DM, Jakobiec FA, "Principles and practice of ophthalmology", Volume 2, Philadelphia, WB Saunders Co, 1994;697-718.). Consequently, when used as suggested by Hoffer and McFarland, fluorescein will not only stain the anterior lens capsule, but also the material below said capsule, particularly as the fluorescein is injected underneath the anterior lens capsule. This means that both the anterior lens capsule as well as the underlying lenticular tissue are stained by the fluorescein dye. Thus, no difference in staining can be observed between the anterior capsule and the underlying tissue during the capsulorhexis, and the desired improved visibility is not, or not sufficiently, achieved.

Moreover, it was noted by Hoffer and McFarland that the sodium hyaluronate, which is used during the operation to fill the anterior chamber of the eye, may become stained and may have to be replaced with fresh sodium hyaluronate.

5 Of course, it is undesired to have to interrupt the course of the surgical procedure to replace the gel layer.

The present invention seeks to overcome the above described problems associated with poor visibility of the lens capsule during cataract surgery. It is an object of 10 the invention to make it possible to visually distinguish the anterior lens capsule from the underlying lenticular material, so that the configuration of an opening in the anterior lens capsule can be better monitored during surgery, for example to prevent the development of a radial 15 tear toward or beyond the equator of the lens capsule during the performance of a capsulorhexis.

Surprisingly, it has now been found that said object may be attained by using a specific dye or mixture of dyes, which is capable of staining tissue or a tissue component, 20 e.g. a membrane, without diffusing through said tissue or component thereof. Hence, the invention relates to a method for performing a capsulorhexis, wherein an anterior lens capsule is stained using at least one dye, which dye is capable of staining tissue without noticeably diffusing 25 into said tissue.

In a method according to the invention, the outer surface of the anterior lens capsule is selectively stained, by which is meant that the lenticular material beneath the anterior lens capsule, is not noticeably 30 stained. Accordingly, during the opening of the anterior lens capsule, a clear distinction can be observed between the portion of the anterior lens capsule, that is being removed, and the underlying lenticular material. This distinction facilitates the controlled opening of the 35 anterior capsule, and reduces the risk of inadvertent

damage to the capsule, for example a radial tear toward or beyond the equator of the lens.

It has been observed that the staining of the anterior lens capsule does not have a detrimental effect on the tissue with which the dye is contacted. Furthermore, it has been observed that shortly after the surgical procedure has been completed, substantially all visible traces of the dye have disappeared. Thus, a patient undergoing a cataract extraction involving a staining of the anterior lens capsule in accordance with the invention experiences no more distress or undesired side effects as when a conventional surgical procedure, not involving staining, is employed.

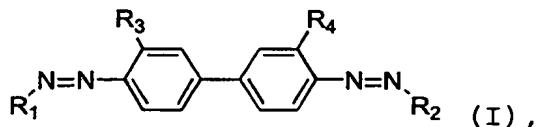
Furthermore, undesired staining of the intraocular structures other than the anterior lens capsule does not, or not to an adverse extent, occur. Staining of the sodium hyaluronate gel, that is applied after rinsing the dye from the anterior chamber, also does not, or not to an adverse extent, occur.

As has been mentioned above, in a method according to the invention, the anterior lens capsule is stained using a dye. An important aspect of the invention is that a dye is used which is capable of staining tissue without diffusing into or through said tissue. Suitable dyes having this capability further should have sufficient coloring, or staining capacity at concentrations which are physiologically and toxicologically acceptable. In other words, the minimum amount of dye which is necessary to provide sufficient staining for a useful coloring to be visible should so be low that no, or hardly any, adverse toxic effects occur. Preferably, the dye is not or hardly endothelial toxic. It is further preferred, that substantially no traces of the dye are present in the eye, shortly after the cataract extraction procedure has been completed. As a result, there is hardly any risk of the

patient experiencing any irritation of the cornea (corneal edema) or another part of the eye.

Particularly good results have been achieved using a dye having the formula (I)

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wherein R_1 and R_2 are the same or different arylgroups, and wherein R_3 and R_4 are independently chosen from hydrogen, methyl, ethyl, methoxy, amino, hydroxyl, and sulfonate. R_1 and R_2 are preferably the same and formed by substituted naphtylgroups. Preferably, the naphtylgroups are substituted with one or more of sulfonate groups, amino groups and hydroxyl groups.

In a highly preferred embodiment, the dye is chosen from the group of trypan blue, trypan red and brilliant crysyl blue. It has been found that these dyes provide a clearly visible staining at very low amounts. Also, they have an extremely advantageous toxicity profile. More preferably, the dye is trypan blue.

Of course it is also possible to use mixtures of the above dyes as long as the resulting mixture is capable of achieving a color of the anterior lens capsule which can be easily distinguished from the color of the material below said capsule.

The dye is preferably used as a physiologically compatible solution. In a particularly preferred embodiment, the dye is formulated in an aqueous salt solution, which is isotone with ocular fluid. The salt is preferably sodium chloride, sodium phosphate, potassium chloride, calcium chloride, magnesium chloride, or a combination thereof. Suitable examples are Balanced salt solution or Hartmann's lactated Ringer's solution (Nuijts RMMA, Edelhauser HF, Holley GP, "Intraocular irrigating solutions: a comparison of Hartmann's lactated Ringer's solution, BSS and BSS plus", Clin. Exp. Ophtamol., vol. 233

(1995), pp. 655-661). In accordance with this embodiment, the salt concentration will be in the range of 0.8 to 1.0 wt.%, based on the weight of the solution.

It is further preferred that the solution has a neutral pH, i.e. a pH between 6.5 and 7.5. The skilled person will be able to select a suitable buffer, which has the properties to be of use in ophthalmic applications. An example of a suitable buffer is phosphate buffered NaCl, commercially available at NPBI, Emmer-Compascuum, The 10 Netherlands

In certain cases, depending on the desired manner of applying the dye solution to the anterior lens capsule, it may be desired to formulate said solution as a dispersion, or a viscous or viscoelastomeric solution, for example 15 hyaluronic acid (see WO-A-96/32929). It will be well within the standard expertise of the skilled person to select a suitable form for the solution. For instance, a higher viscosity may be desired in order to reduce the tension on the lenticular capsule during the capsulorhexis or to 20 protect the cornea.

The concentration of the dye or the mixture of dyes in the solution will preferably be between 0.001 and 2 wt.%, more preferably between 0.01 and 0.1 wt.%, based on the weight of the solution. Within this range, the 25 concentration may be adapted to the toxicity and coloring characteristics of the dye used. It is preferred that such an amount is chosen that an optimal staining effect is achieved, while at the same time the risk of possible damage to the eye or any part thereof due to the toxicity 30 of the dye is minimized.

A method according to the invention is preferably employed as part of a surgical procedure for cataract extraction. After the eye is opened, for example by making a scleral or corneal tunnel incision, the aqueous (ocular 35 fluid) is aspirated and the anterior chamber is filled with air. A few drops of the above described solution comprising

the dye in an appropriate concentration is applied onto the anterior lens capsule. The application of the solution may be carried out by bringing a canula that is attached to a syringe containing the dye into the anterior chamber, and 5 to inject a few drops of the dye, generally less than 1 ml, onto the anterior lens capsule.

The anterior chamber is filled with air, so that the concentration of the dye in the solution is not lowered by the aqueous. As an alternative the dye can be administered 10 in a higher concentration into the aqueous, or a dispersion of the dye in a viscous or viscoelastomeric solution can be used.

Preferably, the excess dye is washed out by irrigating the anterior chamber, leaving a faint but clear staining of 15 the anterior lens capsule, after which the surgery can be continued using routine techniques. The irrigation may be carried out by using Balanced salt solution or any other solution that is commonly used in intraocular surgical procedures.

20 After the anterior lens capsule has been stained, the capsule can be opened using routine surgical techniques. Independent of whether a red fundus reflex is present, the defect in the capsule can be observed because of the difference in color between the stained lens capsule and 25 the exposed, grey-white lens substance. For example, the outline of capsular defect can be visualized during the creation of a capsulorhexis, during removal of the lens substance by phacoemulsification, and during implantation of an intraocular lens in subsequent phases of the surgery.

30 In selected cases that may have an increased risk of the development of after-cataract, a posterior capsulorhexis is made in the posterior lens capsule, before or after the implantation of an IOL. In these cases, a method according to the invention may be employed to stain 35 the posterior lens capsule. Staining of the posterior lens

capsule facilitates a controlled opening of the posterior capsule without damaging the anterior vitreous membrane.

The invention will now be elucidated by the following, non-restrictive examples.

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Example I

1 g of Trypan blue powder (Gurr, BDH Laboratory Supplies, Poole, United Kingdom) is dissolved in 1000 ml (1 liter) of Balanced salt solution (an aqueous solution of 10 0.9% NaCl) to obtain a concentration of 0.1 wt.% dye in solution. From the solution, 0.5 ml is drawn into a syringe, and a canula is attached to the syringe.

Example II

15 An *in-vivo* cataract extraction procedure is carried out on a human eye. A corneal tunnel incision is made, the aqueous is aspirated and the anterior chamber is filled with air. A canula that is attached to a syringe containing the dye solution prepared in accordance with Example I is 20 brought into the anterior chamber. The tip of the canula is held against the anterior lens capsule, and a few drops of the dye solution is applied onto the anterior lens capsule. Then, the anterior chamber is flushed with Balanced salt solution (without dye), until all visible traces of the dye 25 are washed out. A bluish staining of the anterior lens capsule was visible.

30 A visco-elastic substance (HPMC Ocucoat, purchased from Storz, Clear Water, Florida, USA) is injected into the anterior chamber, and with a 30 gauge needle or fine forceps, a capsulorhexis is made. The configuration of the capsulorhexis is controlled by visualization of the blue stained peripheral portion of the anterior capsule, whereas only the gray lenticular mass is seen in the area where the central portion of the anterior capsule has been excised.

After completion of the capsulorhexis, a phacoemulsification procedure is performed to remove the lenticular tissue.

Eur 4628

Claims

1. A method for performing a capsulorhexis, wherein a lens capsule of an eye is stained using at least one dye, which dye is capable of staining tissue without diffusing through said tissue.

5 2. A method according to claim 1, wherein the lens capsule is the anterior lens capsule.

3. A method according to claim 1 or 2, wherein the anterior lens capsule is stained by injecting the dye onto the capsule.

10 4. A method according to any of the preceding claims, wherein the method is part of a surgical procedure for cataract extraction.

15 5. A staining composition suitable for use in a method according to any of the preceding claims, which composition comprises at least one dye which is capable of staining tissue without diffusing through said tissue.

6. A staining composition according to claim 5, wherein the dye is chosen from the group of trypan blue, trypan red and brilliant crysyl blue.

20 7. A staining composition according to claim 5 or 6, wherein the composition has the form of a physiologically compatible solution.

25 8. A staining composition according to claim 7, wherein the at least one dye is present in a concentration between 0.001 and 2 wt.%, based on the weight of the solution.

9. A staining composition according to claims 5-8, which further comprises between 0.8 and 1.0 wt.%, based on the weight of the solution, of a salt.

30 10. Use of at least one dye, which dye is capable of staining tissue without diffusing through said tissue, for

the manufacture of a composition for staining an anterior lens capsule of an eye in a method for performing a capsulorhexis.

INTERNATIONAL SEARCH REPORT

II. International Application No
PCT/NL 99/00284

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K49/00 A61F9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 379 650 A (FARBENINDUSTRIE A G) September 1932 (1932-09) claims 1-3; examples 1,5 ---	5-10
Y	US 4 350 676 A (LATIES ALAN M ET AL) 21 September 1982 (1982-09-21) column 8, line 55 - column 9, line 20; claim 1; table 2 ---	5-10
X	TANIUCHI O.: "Intraocular penetration of trypan blue and of colloidal carbon administered by intraTenon's capsular injection" FOLIA OPHTHALMOL. JPN., 1981, 32/1 (343-350), XP002082491 JAPAN abstract ---	5-10 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

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04/08/1999

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INTERNATIONAL SEARCH REPORT

National Application No
PCT/NL 99/00284

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>NORN M. S.: "Per operative trypan blue vital staining of corneal endothelium. Eight years follow up." ACTA OPHTHALMOLOGICA, vol. 58, 1980, pages 550-555, XP002082492 abstract the whole document</p> <p>---</p>	5-10
X	<p>NORN M. S.: "Vital staining of corneal endothelium in cataract extraction" ACTA OPHTHALMOLOGICA, vol. 49, 1971, pages 725-733, XP002082493 abstract the whole document</p> <p>---</p>	5-10
X	<p>SOLOMON K. D. ET AL: "Protective effect of the anterior lens capsule during extracapsular cataract extraction" OPHTHALMOLOGY, vol. 96, no. 5, May 1989 (1989-05), pages 591-597, XP002082494 abstract page 593, column 2</p> <p>-----</p>	5-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/NL 99/00284

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-4 because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1 (iv) PCT- Method for treatment of the human or animal body by surgery
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/NL 99/00284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 379650	A	NONE	
US 4350676	A	21-09-1982	
		CA 1193967 A	24-09-1985
		EP 0066937 A	15-12-1982
		JP 57197216 A	03-12-1982